Attorney Docket No. PC10015AJTJ

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Murray C. Maytom et al. :

APPLICATION NO.:09/248,438 : Examiner:

FILING DATE: February 11, 1999 : Group Art Unit:

TITLE: Method Of Treating Impotence Due To Spinal Cord Injury :

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 CFR 1.131

I, Murray Craig Maytom, Declare that:

1. I attended: (1) the University of Cape Town, South Africa, from 1979 to 1985, obtaining the degree of Bachelor of Science in Anatomy in 1983 and the degree of MBChB in 1985; and (2) the Graduate School of Business, Cape Town, South Africa, from 1991 to 1992, where I was awarded a Masters Degree in Business Administration. I was also awarded a Diploma in Anaesthetics (FFA Pt.1) by the London Royal College of Surgeons, United Kingdom in 1989.

2. I have worked for Pfizer Inc. since 1994. My current title is Medical Director, VIAGRA®, World Wide Team, Pfizer Inc.

3. I am an inventor in the above-identified U. S. patent Application, No. 09/248,438, filed on February 11, 1999. The application claims priority to provisional application 60/075,580, filed February 23, 1998.

4. The invention is directed to the treatment of erectile dysfunction (ED) in patients with an injured spinal cord. I am aware that the application currently stands rejected, in part,

over Derry et al. (Neurology, 1997, Vol. 48, No. 3, page A215). The Derry abstract discloses a publication date in March of 1997.

5. Prior to March, 1997, the date of the Derry publication, under my guidance and control, a clinical study was conducted to assess the efficacy and safety of oral doses of UK-92,480 in spinal cord injury (SCI) patients with erectile dysfunction, as evidenced by the copy of the experimental protocol, attached hereto as Exhibit 1. UK-92,480 is the internal Pfizer designation for the cGMP PDE_V inhibitor sildenafil, currently marketed as the citrate salt under the registered trademark VIAGRA®.

6. The results from the above-mentioned study, which was completed prior to March 1997 are as follows: Twenty six patients with spinal cord injury were evaluable. Nine of twelve patients treated with sildenafil and one of fourteen patients treated with placebo reported that their treatment had improved their erections. Eight of twelve sildenafil patients and two of fourteen placebo patients wanted to continue taking their treatment. Analysis of sexual function questionnaire responses also indicated a significant improvement in satisfaction with sex life for sildenafil patients compared with placebo patients.

7. The above-described clinical study, evidenced by the protocol and the data reviewed above, demonstrates that I made the invention of the claims, i.e., a method of treating ED in SCI patients by administering a cGMP PDE_V inhibitor to such patients, prior to March of 1997.

8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Murray C. Maytom

2.7.02

Date

ERECTILE DYSFUNCTION: PROTOCOL 148-358-000

A TWO STAGE DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF ORAL DOSES OF UK-92,480 IN SPINAL CORD INJURY PATIENTS WITH ERECTILE DYSFUNCTION.

PRINCIPAL INVESTIGATOR:

CO-INVESTIGATOR:

LOCATION OF STUDY:

LOCATION OF LABORATORY:	Laboratory Safety Data Analysis Hazleton Laboratories (Europe) Ltd Otley Road, Harrogate North Yorkshire HG4 1PY Tel: (0423) 500011
SPONSOR:	Central Research, Pfizer Limited, Ramsgate Road, Sandwich, CT13 9NJ
PFIZER CPM:	Dr M C Maytom Tel: (0304) 618613 Outside hours: (0304) 616161
PFIZER CRA:	Ms M Cuddigan Tel: (0304) 618677 Outside hours: (0304) 616161
PROJECTED START DATE:	[redacted]
PROJECTED FINISH DATE:	[redacted]

TABLE OF CONTENTS

2. INTRODUCTION

2.1 Review of UK-92,480

Mode of Action

UK-92,480 is a selective inhibitor of cyclic GMP specific phosphodiesterase (PDE) type V. PDE_V represents the predominant PDE in corpus cavernosum smooth muscle and is also found in platelets and blood vessels. Sexual stimulation leads to rises in nitric oxide (NO) which in turn elevates cGMP through activation of guanylate cyclase, causing cavernosal smooth muscle relaxation. Animal studies indicate that erection resulting from the relaxation of corpus cavernosum smooth muscle, mediated by NO via cGMP, is enhanced by UK-92,480 due to inhibition of the breakdown of cGMP.

Toxicology

Oral UK-92,480 has been administered for 6 months to both rats and dogs. In rats, doses of 12 and 60mg/kg/d produced mild changes to liver, thyroid and adrenals whilst 3mg/kg/d had no effects. In dogs, doses of 50mg/kg/d produced pharmacological effects on the cardiovascular system whilst 3 and 15mg/kg/d had no effects. The changes in both species were either of an adaptive or mild nature and not indicative of overt toxicity. The dose selected for this study in men with spinal cord injury is less than 1mg/kg/d.

Clinical Data - Volunteer Studies

UK-92,480 has been administered to over 200 male subjects, including 164 healthy volunteers, as single and multiple doses.

When administered to healthy volunteers in the fasted state UK-92,480 is rapidly absorbed with peak plasma concentrations occurring in less than one hour. The mean absolute bioavailability is 41%. UK-92,480 is extensively and rapidly metabolised with a terminal phase half-life of approximately 4 hours.

Single oral doses up to 50mg have been well tolerated. At single doses greater than or equal to 100mg, mild to moderate headaches and flushing were recorded, and at single doses of 150mg and 200mg transient disturbance of colour vision was reported.

Multiple oral doses of 25mg tid for 10 days were well tolerated however multiple doses of 50mg tid and 75mg tid for 10 days were poorly tolerated by some subjects because of back pain and myalgia and/or symptoms of indigestion.

Clinical Data - Patient Studies

In a pilot multiple dose efficacy study (148-350), 16 patients with erectile dysfunction (with no obvious organic cause) received a dose of 25mg tid for 7 days in a placebo controlled crossover study. UK-92,480 was effective in improving erectile function. Some patients experienced mild and transient myalgia and some noted indigestion during active treatment.

In a subsequent pilot efficacy study (148-351) single doses of UK-92,480 (10, 25, and 50mg) were administered to 12 patients with erectile dysfunction and were effective in enhancing the erectile response to visual sexual stimulation. The medication was well tolerated with all adverse events, being minor and transient, and none leading to patient withdrawal from the study.

In summary, UK-92,480 has been well tolerated at single oral doses up to 50mg and has shown promising efficacy at these dose levels in patients with erectile dysfunction.

Further details are provided in the Investigator's brochure dated November 1994.

2.2 Rationale for study

There is a need to assess whether UK-92,480 taken as required (not more than once daily), improves erectile function in men with spinal cord injury (SCI), and whether this effect translates into improved sexual function in the domestic setting .

Preliminary data suggest that doses of 50mg will be effective and well tolerated in patients with non-organic causes of ED. Therefore the dose selected for this study is 50mg.

3. PURPOSE OF STUDY

3.1 Primary objectives

- To determine the proportion of patients in each of the treatment groups who at the end of Part II would be willing to continue to use their randomised treatment.
- To assess the safety and toleration of oral doses of UK-92,480 taken as required (not more than once daily) over a period of 4 weeks.

3.2 Secondary objectives

- To determine the proportion of patients in each of the treatment groups who have an improvement in sexual function at the end of Part II.
- To determine the proportion of patients in each of the treatment groups whose partner indicates an overall improvement in the patient's erections at the end of Part II.

4. ETHICS COMMITTEE REVIEW AND INFORMED CONSENT

4.1 Review of study ethical considerations

This clinical trial will be conducted according to the current revision of the Declaration of Helsinki (Revised Hong Kong 1989) and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

The clinical trial protocol will be approved prior to its start by an Ethics Review Committee, whose constitution is appropriate for the country in which the clinical trial

self-injection programme may be entered provided that they are also able to achieve a full or partial erection in response to vibratory stimulation (criterion 5.2.4), and do not inject during the study or in the week before they are screened to enter the study.

5.2.4 Patients who during the study screening are able to achieve at least a grade 2 (see section 8.1) erection in response to stimulation with a vibrator.

5.3 Exclusion criteria

5.3.1 Patients with associated genital anatomical deformities (congenital or acquired e.g. penile fibrosis) causing erectile dysfunction, or known or suspected vascular or endocrine causes of erectile dysfunction.

5.3.2 Patients taking drugs which have been causally associated with erectile dysfunction, may enter the study provided that the dose remains unchanged for a period covering a month prior to screening and for the duration of the study.

5.3.3 Patients with documented major haematological, renal or hepatic abnormalities, based on history and/or results of laboratory tests performed at the screening visit (see Appendices D & E). Abnormalities of doubtful clinical significance will be discussed with a Pfizer representative prior to inclusion of that patient.

5.3.4 Patients with diabetes mellitus.

5.3.5 Patients with a history of stroke, subarachnoid haemorrhage, bleeding disorder, or active peptic ulceration.

5.3.6 Patients considered by the investigator to be at risk from a hypertensive response due to autonomic dysreflexia on use of the vibrator (in particular SCI men with injuries at or above the T5/6 spinal cord level).

5.3.7 Patients with known postural hypotension or a resting sitting blood pressure < 90/50mm Hg.

5.3.8 Patients receiving nitrates or anticoagulants.

5.3.9 Patients who have received any experimental drug within the past three months.

5.3.10 Patients who regularly drink more than 28 units of alcohol per week (1 unit=½ pint of beer, $^1/_5$ th gill of spirits or 1 glass of wine).

5.3.11 Patients who, in the opinion of the investigator, are unlikely to complete the diary satisfactorily.

5.3.12 Patients who have evidence of any medical, psychological or social condition which would impair their ability to take part in the study, or which would increase the risk to themselves by participating. Patients who are clinically depressed must

Each bottle will be labelled as follows:

Label	Flag
Pfizer Study: 148-358	Pfizer Study: 148-358
Patient Number: *	Patient Number: *
Bottle ID: **	Bottle ID: **
Contents: 2 capsules of either UK-92,480 (25mg) or placebo	
Take both capsules Expiry date:	
FOR CLINICAL TRIAL USE ONLY	
KEEP OUT OF THE REACH OF CHILDREN	

* 1 - 100
** A1 or A2

<u>Part II double-blind, randomised, placebo-controlled, parallel group study</u>

Medication will be supplied as a single bottle containing 56 capsules (either UK-92,480 or placebo).

Each box will be labelled as follows:

Label	
Pfizer Study: 148-358	
	FOR CLINICAL TRIAL USE ONLY
Patient Number: *	
	KEEP OUT OF REACH OF CHILDREN
Contents: 1 bottle	
	Expiry Date:

6.3 Drug Administration

Part I:
The single dose (2 capsules) will be taken by the patient under supervision while attending the clinic. The patient will be fasted at the time of dosing and monitoring will be performed in a private room.

Part II:
Each dose will be taken by the patient on an out-patient basis. At Visit 3, the investigator will give the following dosing instructions:

- The single dose of 2 capsules can be taken as required, but must not be taken more than once per day.
- The dose can be taken at any time during the day.
- If the patient wishes to have sexual activity on a particular day, then he should take the dose approximately an hour in advance.
- The patient should record the actual date and time of dosing in the diary provided.
- If on a particular day, the capsules are taken close to midnight, there must be a period of at least 4 hours before the patient can take the study medication again.
- The capsules should be swallowed whole with a glass of water.
- The capsules may be taken with food or in the absence of food.
- Patients should be advised not to drink more than 2 units of alcohol within one hour of sexual activity, since alcohol may impair the patient's ability to have erections and cause the treatment to be less effective.
- It is recommended that patients try to take the study medication at least once a week over the 4 week period of the study.

6.4 Drug accounting

The investigator will be responsible for recording the receipt and administration of all drug supplies, and for ensuring the supervision (via a hospital pharmacist) of the storage and allocation of these supplies. At intervals, as appropriate, or upon completion of the study, all unused drug supplies and empty containers must be returned to Pfizer Central Research. Collection of these drugs will be undertaken by the Clinical Research Associate (CRA) from Pfizer, who will also be allowed at intervals, and upon request, during the study, to check unused supplies.

6.5 Drug storage

Study drug supplies should be stored securely in conditions where the temperature will not exceed 30°C.

7. PATIENT VISITS

The following sections list the activities/procedures to be carried out by the investigator (not necessarily in the order listed) at each visit of the patient to the clinic.

In patients considered suitable to continue in the study, the following will also be performed:

- Blood for safety laboratory tests for haematology and biochemistry.
- Sealed Partner Questionnaire to be given to the patient's partner.
- Patient to complete Sexual Function Questionnaire
- Inform patient of appointment for Visit 2, and instruct the patient not to eat or drink for two hours before the appointment.

The investigator will exclude a patient from the study if:

1. The patient did not have a suitable erectile response (at least grade 2) on stimulation by vibrator, or if the patient demonstrated a hypertensive dysreflexic response to the vibrator that the investigator considers puts the patient at risk.
2. The patient does not otherwise fulfil the entry criteria.

7.2 Part I - Placebo-controlled, Double-Blind, Randomised, Single dose two way cross-over study

For the first part of the study (Visits 2 and 3), the patient will be fasted, and the procedures will be carried out in a private room, with the investigator or an experienced assistant constantly in attendance.

As at the screening visit, the Rigiscan will be applied and the monitoring started at least 5 minutes before the dose is given. With the patient lying supine, the vibration will be applied to the frenulum of the penis at 0.5, 1.0 and 1.5 hours post-dose and using the same settings (frequency, amplitude) established at the screening visit. The vibrator will be applied until an erection occurs, or for 4 minutes, whichever is shorter.

At each stimulated erection, the duration of application of the vibrator and the patient's assessment of the erection achieved, will be recorded.

Throughout each visit, the patient will be attached to an automatic B.P. cuff to allow instant B.P. readings if necessary. Personnel, equipment and medication to manage an acute hypertensive response, will be immediately accessible.

7.2.1 Visit 2

Only patients who the investigator has assessed as meeting the criteria for inclusion into the study will participate.

List of activities/procedures for this visit:

- Physical examination
- Give patient medication (time of dosing recorded) and at 0.5, 1.0 and 1.5 hours post-dose record the erectile response to vibrator using a Rigiscan, and the patient Grading Scale.

7.3 Part II - Double-Blind, Randomised, Placebo-controlled, Parallel group study over 4 weeks

The second part of the study will last four weeks and will commence four days after Visit 3. During this period, the patient will take the study treatment as required (up to a maximum of once daily) about an hour prior to sexual activity. It is recommended that the patient attempts to take the medication at least once every week, over the 4 week study period. At the end of the study period the patient will return to the clinic for study Visit 4.

7.3.1 Visit 4

List of activities/procedures for this visit:

- Physical examination, sitting blood pressure and pulse rate
- Review Diary and attempt to clarify reasons for any missing or ambiguous data
- Record concomitant medication and adverse events
- Ensure patient has returned unused study medication (the investigator will disqualify from any follow-on studies any patient who fails to return study drug supplies or who fails to account for any missing medication)
- Blood for safety laboratory tests (15ml for haematology and biochemistry)
- Patient to complete Sexual Function Questionnaire and End of Treatment Questionnaire
- Sealed Partner Questionnaire to be given to the patient's partner

7.3.2 Visit 5 - Follow-Up Visit

The follow-up visit will take place 2 weeks after Visit 4.

List of activities/procedures for this visit:

- Physical examination, sitting blood pressure and pulse rate
- Record adverse events
- Blood for safety laboratory tests (15ml for haematology and biochemistry)
- Confirm that there is no outstanding study medication/documentation.
- Assessment for inclusion into an extension study.

8. STUDY EVALUATIONS

8.1 Diary

The patient will complete a Diary (designed to capture information on dates and times of dosing and of erectile activity) throughout Part II of the study. Patients will be asked to record details of erections associated with sexual stimulation, including approximate time of onset, rigidity and whether the duration of the erection was sufficient for sexual activity.

8.4 Pharmacokinetic Samples

The serum samples collected in Part I of the study will be centrifuged and refrigerated at -20ºC at the investigator site. They will be collected, frozen and stored by the investigator. The samples will be sent for analysis to determine the plasma drug concentrations.

9. SAFETY ASPECTS

9.1 Adverse events

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to study drug will be recorded on the Adverse Event pages of the case report form. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbations of pre-existing illnesses should be recorded. Objective test findings (e.g. abnormal laboratory test results) that result in a change in study drug dosage should also be recorded.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer (see section 9.2). Follow-up of the adverse event, even after the date of therapy discontinuation, is required if the adverse event or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilise at a level acceptable to the investigator and the Pfizer clinical monitor (CRA/CPM).

9.2 Serious Adverse Events

All serious adverse events eg. side effects, laboratory abnormalities, other safety tests (eg. ECG) or intercurrent illnesses which occur during the study until the last follow-up visit required by the protocol, or until 30 days after the last dose of study drug, whichever comes later, regardless of treatment group or suspected relationship to drug, must be reported immediately by telephone to the Pfizer Clinical Research Associate (0304) 618677 or Clinical Project Manager (0304) 618613.

Serious adverse events include any experience that suggests a significant hazard, such as events which:

- are fatal
- are life-threatening
- result in permanent disability
- require in-patient hospitalisation or prolongation of a hospital stay
- involve cancer, a congenital anomaly or drug overdose

It should be emphasised that, regardless of the above criteria, any additional adverse experience which the investigator considers serious should be immediately reported.

be followed up with appropriate medical management until there is a return to normal or baseline values or a clinical diagnosis of intercurrent illness is confirmed. The investigator should record comments on any clinically significant abnormalities in the Case Report Forms.

9.4 Discontinuation from study (withdrawals from study)

The reason for a patient discontinuing from the clinical trial will be recorded in the case report form. A discontinuation occurs when an enrolled patient ceases participation in the clinical trial, regardless of the circumstances, prior to completion of the protocol. A discontinuation must be reported immediately to the Pfizer clinical monitor (CRA/CPM) if it is due to a serious adverse event. The final evaluation required by the protocol will be performed just prior to study drug discontinuation, if possible. Otherwise, final evaluation will be performed as soon as possible after study drug discontinuation. The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up (if required) for such patients, and document the course of the patient's condition.

9.5 Additional safety tests

A full medical examination, including body weight and height will be carried out at screening. The medical history will include details of previous treatment and of any penile fibrosis or plaques. The physical examination will include an assessment of genitalia and the investigator will record the presence of any penile fibrosis or plaques.

Blood pressure and pulse rate measurements will be taken in the sitting position. Blood pressure and pulse rate measurements will be taken using an automated BP cuff (ideally with a printout facility) before and after the study assessments both at screening and during the Part I visits (Visit 2 and Visit 3). Any other recordings taken during the assessment are discretionary, but must be documented if performed.

Blood samples (15ml) for routine haematological and biochemical testing will be taken at screening and at Visits 4 and 5. Results from the range of laboratory tests described in Section 9.3 will be reviewed prior to inclusion in the study. Provided the results of the tests are satisfactory and all the entry criteria are fulfilled, the patient may enter the study.

At each visit, the investigator will obtain any information about concurrent illness and any therapeutic interventions (e.g. drug therapy, surgery etc.), and record this on the CRF. Included, where applicable, will be the diagnosis and the dates of onset and remission of all illnesses, as well as the name, daily dose taken and dates of any drug therapy, whether prescribed by a physician or not.

9.6 Drug Blinding Code

The double-blind supplies are provided to the investigator with a sealed copy of the randomisation which allows the investigator to break the treatment code for an individual patient. This must be kept in a secure place for inspection by Pfizer from time to time during the course of the study and will be collected by the monitor at the end of the study.

care. The investigator should ensure that the card is returned by the patient at the end of the study.

10. STATISTICAL METHODS

10.1 Justification of study numbers

In study 148-351, ten out of twelve patients with non-organic erectile dysfunction indicated that UK-92,480 had improved their erections, whereas ten out of twelve failed to indicate an improvement on placebo.

A triangular test (Whitehead J, 1992, The Design and Analysis of Sequential Clinical Trials, 2nd Ed., Ellis Horwood, Chichester) using a two sided significance test with a working significance level of 5%, 80% power when the true response rates are 60% on UK-92,480 and 25% on placebo, inspections every four responses, and equal allocation to each treatment has the following characteristics (all fractional sample sizes have been rounded up to the next largest integer):

Response rates				Expected	Median	90th percentile
Active	Placebo	c+	c-	sample size	sample size	sample size
0.250	0.250	0.025	0.025	39	35	60
0.327	0.250	0.101	0.012	43	39	66
0.414	0.250	0.283	0.005	45	43	67
0.507	0.250	0.553	0.002	44	42	65
0.600	**0.250**	**0.800**	**<0.001**	**39**	**37**	**59**
0.686	0.250	0.938	<0.001	33	30	51
0.761	0.250	0.986	<0.001	27	24	42

c+ is the probability that UK-92,480 is found to be significantly superior to placebo at a two sided significance level of 0.05.

c- is the probability that UK-92,480 is found to be significantly inferior to placebo at a two sided significance level of 0.05.

The maximum sample size will be 88. The equivalent fixed sample size for a conventional parallel group study would be 57.

The endpoint used in the triangular test will be the response to question B in the End of Treatment Questionnaire.

10.2 Randomisation method

Prior to the start of the study, patients will be allocated to one or other of the sequence groups in Parts I and to one or other of the treatment groups in Part II by means of a computer generated pseudo-random code, using the method of random permuted blocks. The randomisation will not be stratified.

- Erectile response assessed by the patient (grade and duration), and by Rigiscan (duration of rigidity above 60% and above 80%) following stimulation with a vibrator in Part I.

The secondary measures of efficacy are:

- The proportion of patients in each of the treatment groups who, at the end of Part II (Visit 4), indicate in the questionnaires that their sexual function has improved.

- The proportion of patients in each of the treatment groups whose partners, at the end of the Part II visit (Visit 4), indicate in the confidential questionnaires that they perceive that the patient's erectile function has improved.

Logistic regression will be used to analyse proportions. Standard ANOVA methods will be used to analyse the erectile responses. Analyses of the Part I data will follow standard methodology for the analysis of two period, two treatment crossover trials and allow for effects due to treatment, period and sequence group. The analyses for Parts I and II will also include any additional covariates which are deemed to be appropriate.

The terminal analysis of question B in the End of Treatment Questionnaire, will allow for its use in the sequential procedure described above. The analyses of all other response variables will be unadjusted.

If the assumptions of the above analysis methods are not met, then alternative methods will be used, and the reasons for such variations to the planned analyses will be fully documented.

Safety data will be subject to clinical review and summarised by appropriate descriptive statistics.

11. PATIENT MANAGEMENT

11.1 Concomitant illness and medication

At each visit, the investigator will obtain any information about concomitant illnesses and any therapeutic interventions, e.g. drug therapy, surgery, etc. Included, where applicable, will be the diagnosis and dates of onset and remission of all illnesses, as well as the name, daily dosage taken, and dates, whether physician-prescribed or not date(s) and description of surgery etc.

11.2 Patient indemnity

Indemnification of the study centre has been supplied by Pfizer Central Research in accordance with U.K. laws.

12.4 Study stopping rules

Modification of Study Design

It is possible that the study may be stopped earlier than expected or that the study design will be modified for reasons that are independent of efficacy findings. These include, but are not restricted to, the following:

1. The determination (possibly from other data) that an inappropriate dose or regimen is being used in the study.
2. Unexpected problems with potential toxicity, either in this study, or from other data.
3. Financial or other resources no longer being available for the project.

In addition, recruitment may be curtailed at a centre for reasons such as:

1. Unacceptably slow recruitment.
2. Evidence that patients in the centre are not in compliance with the protocol, and the investigator is unable to correct the situation.

12.5 Retention of Study Data

The investigator will ensure that all data from patient visits are entered promptly, **in black ball point pen,** on the case record form in accordance with the specific instructions supplied. An explanation for the omission of any required data should appear on the appropriate page.

Every page of the case record form should be signed by the person who completed it along with the principal investigator or his/her approved associate. The principal investigator must sign the final page of the case record form, thereby stating that he/she takes responsibility for the accuracy of the data in the entire case record form.

The central laboratory used at each site will provide, before the study starts, a list of the reference ranges for all laboratory tests to be undertaken and details of the method used for quality control. These will be held by the investigator and a copy sent to the Pfizer CRA. The methods employed for each assay should be available on request. Any change in the laboratory, its procedures, references values etc. during the study must be notified promptly to Pfizer Central Research.

The investigator must arrange for the retention of the patient identification codes (ie. hospital/unit code, trial/study identification code and randomisation number) for at least 15 years after completion or discontinuation of the clinical trial. Other source documents such as patient files, clinic case notes, must be retained for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years after the completion or discontinuation of the clinical trial.

The investigator will also be required to retain his/her copies of the CRFs and other study documentation for this period of time.

SECTION 13 - APPENDIX A

FLOWCHART

		Screening	Part I		Part I		Part II	Follow-up
	Week Visit	-2 1	0 2		1 3		5 4	7 5
1	Informed consent	*						
2	Check inclusion/exclusion criteria	*	*	*3*	*	*3*		
3	Demography	*		*D* *A*		*D* *A*		
4	Physical examination	*	*	*Y*	*	*Y*	*	*
5	Sitting blood pressure and pulse rate	*	*	*W* *A*	*	*W* *A*	*	*
6	Laboratory safety tests	*		*S* *H*		*S* *H*	*	*
7	PK bloods *		*	*O* *U*	*	*O* *U*		
8	Penile Plethysmography	*	*	*T*	*	*T*		
9	Investigator Reviews Diary						*	
10	Patient Sexual Function Questionnaire	*					*	
11	Partner Questionnaire	*					*	

* A single serum sample will be taken at 1.5 hours post dosing- immediately after the erectile response has been graded.